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GASTROENTEROLOGY

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Guest Editorial

DR. BURRILL B. CROHN

Dr. B. B. Crohn, born in 1884, has been practising medicine for 65 years. During this period he has made outstanding contributions in the field of Gastroenterology. He reported in 1932, a new entity, regional ileitis, which is now named after him, "Crohn's disease." He has been a member of many societies as well as being past president of the American Gastroenterological Association. Still with eager vitality, he is Consultant in Gastroenterology to Mt. Sinai Hospital, N.Y., and Columbia University Graduate School of Medicine.

In the history of medicine most of the important discoveries have been made at the bedside by medical (rather than by surgical) clinicians. In the recent decades so called "chronic appendicitis" was the "discovery" of the surgeons, a disease that never existed. Had the surgeons in removing the innocent offender moved their fingers a very few inches to the left they would have palpated the obvious mass of regional ileitis.

The recent over emphasis on laboratory data has tended to overshadow, even at times to eliminate physical findings particularly in the abdomen. Again and again one listens to ten minutes of laboratory details while the demonstrator forgets to mention the palpation of the abdomen which is the essential of abdominal pathology.

Sociological medicine is the emphasis of the modern medical graduates and correctly so, for the complaints in approximately eighty percent of the patients in all subdivisions of internal medicine are functional rather than based on organic disease.

Without in any manner tending to denigrate the important value of laboratory data (often redundant, time consuming, expensive in money and in bed occupancy) the prime essential of good practice, today as was always, is the careful bedside physical findings with the correlation of these findings with the relevant laboratory and radiographic data.

Dr. Burrill B. Crohn

This issue of the University of Toronto Medical Journal is devoted to Gastroenterology and mainly to the long tubular tract from os to anus. Recent volumes have covered the roles of the accessory organs, liver and pancreas.

Included herein is a novel approach to gas dynamics from aerophagia to flatus. There is also a comprehensive review of an entity increasing in importance from one year to the next — carcinoma of the colon. To complete the general topics we have an article on a possible substitute to the gastro-intestinal tract — intravenous hyperalimentation.

Several clinical cases are presented to punctuate the varied roles the gastro-intestinal tract plays in medicine. With Dr. B. B. Crohn as guest editor it is only fitting to have a case presentation of Crohn's disease. And to make things more interesting the patient also had Kallmann's syndrome. The two clinical pathological conferences emphasize the importance of intestinal symptoms and signs as they relate to systemic diseases.

I. Horowitz

Total Parental Nutrition

L. H. Rossman, 7T2

Not for renewal but for eating's sake,
They stuff their bellies with tomorrow's ache.

EDMUND VANCE COOKE

INTRODUCTION

The concept of total parenteral nutrition as a therapeutic and research tool is new to medical science. This article proposes to discuss briefly the technique itself, its historical development, and where some of its applications may lie. As with any new procedure, many centres have developed their own modifications. In this short review I shall describe the catheter technique first developed by Dudrick and his co-workers in Philadelphia and discuss the two general types of nutrient solutions used in major medical centres.

DEFINITIONS

True total parenteral nutrition (TPN) is defined as: the maintenance of the total nutritional requirements including glucose, amino acids, fats, minerals, and vitamins by the intravenous route.

Intravenous hyperalimentation (IVH) is a term which occurs frequently in the literature. It may be defined as: the delivery of hypertonic glucose, protein hydrolysates or crystalline amino acid solutions, and supplementary minerals and vitamins into the superior vena cava in amounts *greater* than required for nutritional equilibrium. This is the commonest technique now in use and much of this article refers to IVH.

HISTORICAL DEVELOPMENT

It is not the purpose of this article to outline the complete history of intravenous therapy. The concept of TPN however should be viewed within the perspective of time. Harvey's description of the circulatory system in 1616 signalled the birth of the idea of feeding those patients unable to eat normally by the intravenous route. One of the earliest intravenous infusions was carried out by Sir Christopher Wren, who in 1656 administered ale, wine and opium into dog's veins using a goose quill attached to a pig's bladder as his apparatus.[8] It was from these crude beginnings that modern intravenous techniques were to evolve.

Advances in bacteriology, physiology, biochemistry, and medical technology, spanning centuries had allowed by the early 1960's the concept of a total life support parenteral system to be thought of in realistic terms. Parenterally administered electrolyte, carbohydrate, and amino acid nutrient solutions had been used for years. The subsequent development of intravenous vitamin preparations and fat emulsions gave the parenteral diet all the components of that taken orally. However prior to 1967 no system had demonstrated its ability to maintain anabolism and growth over long periods. Although adequate nutrient solutions were available, two problems of major importance remained:

1) A method of infusion was required such that hypertonic solutions of adequate caloric intake could be tolerated. Such solutions had proved too irritating to the walls of peripheral veins and thrombosis inevitably resulted.

2) A method was needed which could be used for prolonged periods without undue risk of infection to the patient.

The breakthrough occurred in an historical animal experiment first described by Dudrick, Rhoads, and Vars in 1967[5]. Their work showed that the growth and development of beagle puppies receiving all their nutrition intravenously for periods of up to 36 weeks was similar to control animals who were nourished orally. (Figures 1, 2.) The technique they used involved continuous infusion with a 30% solution of glucose, amino acids, electrolytes, vitamins and trace minerals through a catheter placed in the superior vena cava.

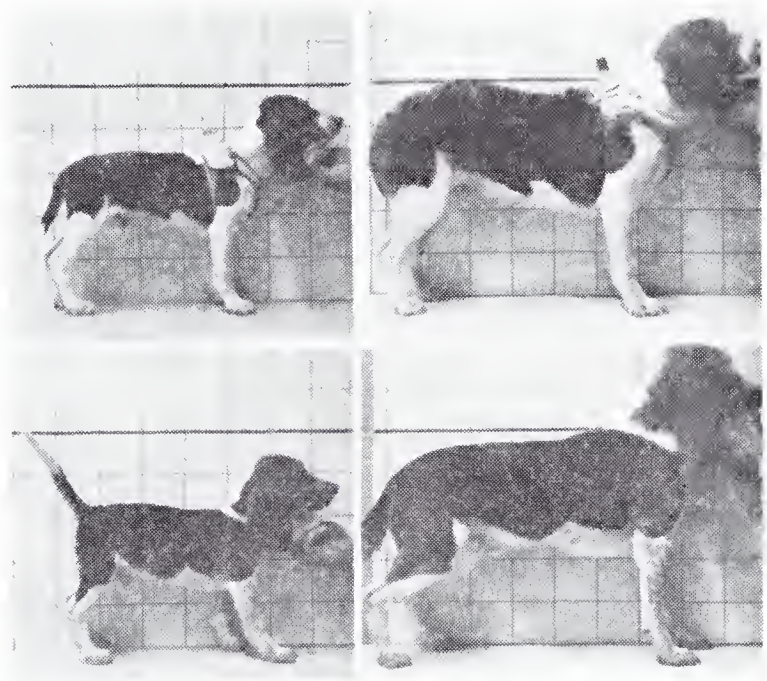

FIGURE 1: Growth and development maintained in animal nourished entirely by vein (at top) over 30-week study compared with oral control littermate (at bottom). Reproduced with the permission of JAMA and Dr. S. Dudrick.

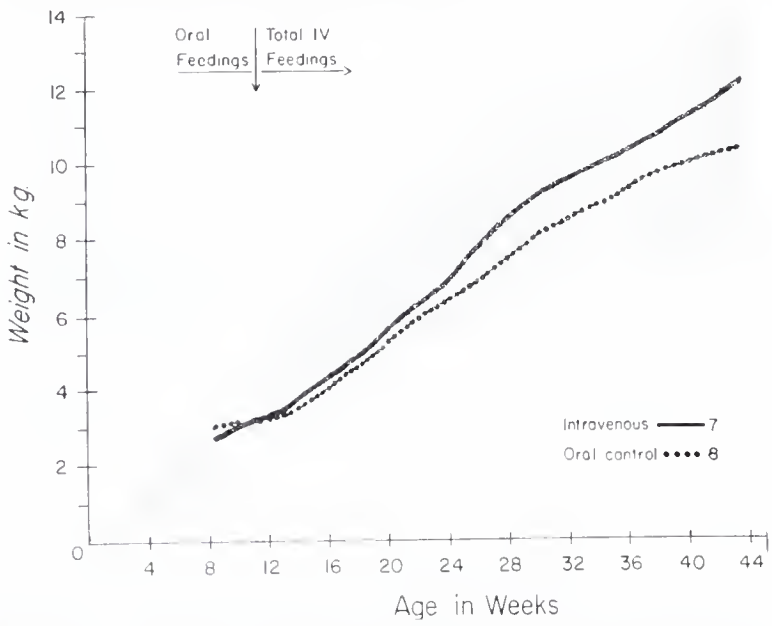

FIGURE 2: Similar weight gains in littermate puppies fed entirely by vein or by mouth from 12 to 42 weeks of age. Normal range of weight gain for beagles (stippled area). Reproduced with the permission of JAMA and Dr. S. Dudrick.

In the face of these results it was not long before a modified version of this technique was utilized in the human. The first such adaptation was attempted on an infant with small bowel atresia. The defect was massive, extending from the ligament of Treitz to within 3 cm. of the ileocecal junction and with partial atresia of the colon. Following massive resections on the fourth day of life intravenous feeding was attempted via the usual route and plasma, 10% glucose and protein solutions were administered. At birth the child had weighed 2.36 kg. and despite therapy her weight continued to fall — reaching 1.8 kg. on day 19. By this time the child was unresponsive and lethargic. In the face of the grim prognosis the prospect of the new technique was considered with the ultimate hope that given time bowel function might compensate and eventually permit adequate enteral nutrition. The results at 45 days are shown in Figure 3.

FIGURE 3: Growth and development of infant nourished completely by vein. At top before feeding; at bottom after 45 days on new feeding regime. Reproduced with the permission of JAMA and Dr. S. Dudrick.

By the 45th day the child's weight had increased to 3.4 kg. and her body length, head circumference, and chest circumference all showed substantial increases[8,15]. This was the first demonstration of long-term total parenteral nutrition with growth and development in humans. The child continued to grow for some time on this regime and managed to survive over a full year, eventually achieving a maximum weight of 8.4 kg.

These results made it apparent that the major problems of parenteral therapy mentioned previously had been overcome. The technique has subsequently been applied to many clinical situations, some of which will be discussed below.

TECHNIQUE

In the interest of completeness a brief description of catheter placement, infusion apparatus and basic parenteral solutions are given here.

Infraclavicular percutaneous catheterization of the superior vena cava by way of the subclavian vein has proven to be the best technique in adults and children over 10 pounds[6]. Infants less than 10 pounds have very small subclavan veins and catheterization is performed through the internal or external jugular veins. The procedure is best performed with the patient in the Trendelenburg position to promote maximum filling of the subclavian veins. With a large needle inserted in the vein a radiopaque catheter is passed through and advanced until it lies within the superior vena cava (best confirmed radiographically). The proximal end of the catheter is attached to standard intravenous tubing and the needle withdrawn. Ideally the procedure is carried out using strict aseptic techniques with proper skin preparation, draping of the area, and utilization of sterile gloves and instruments[4,6,9].

The superior vena cava is used since as a large diameter high flow vessel the infusion of hypertonic solutions is well tolerated by the vessel walls due to rapid dilution of the infusate. Hypertonic solutions are highly irritating to vessel walls and in slower flowing peripheral vessels thrombosis inevitably occurs.

Figure 4 is a diagrammatic illustration of an infusion apparatus. It is intended to demonstrate certain features which have been incorporated into many of the different systems now in use.

Constant infusion of nutrients has provided maximum benefit to patients.[8] The Millipore filter (pore size — 0.22 microns) removes microorganisms which may have contaminated the infusion. A two-channel system has been suggested so that while nutrient mixtures can remain standardized, electrolytes and fluids can be varied to suit the patient's needs. This arrangement is particularly important in those patients with severe burns or large fistula fluid losses.

Although various types of solutions have been developed there are in fact two basic types of infusion. The most widely used solutions are a modification of the type first used by Dudrick[6,8]. An example of this type is presented in Table 1. On this regime sufficient carbohydrate can be supplied to block breakdown, sufficient

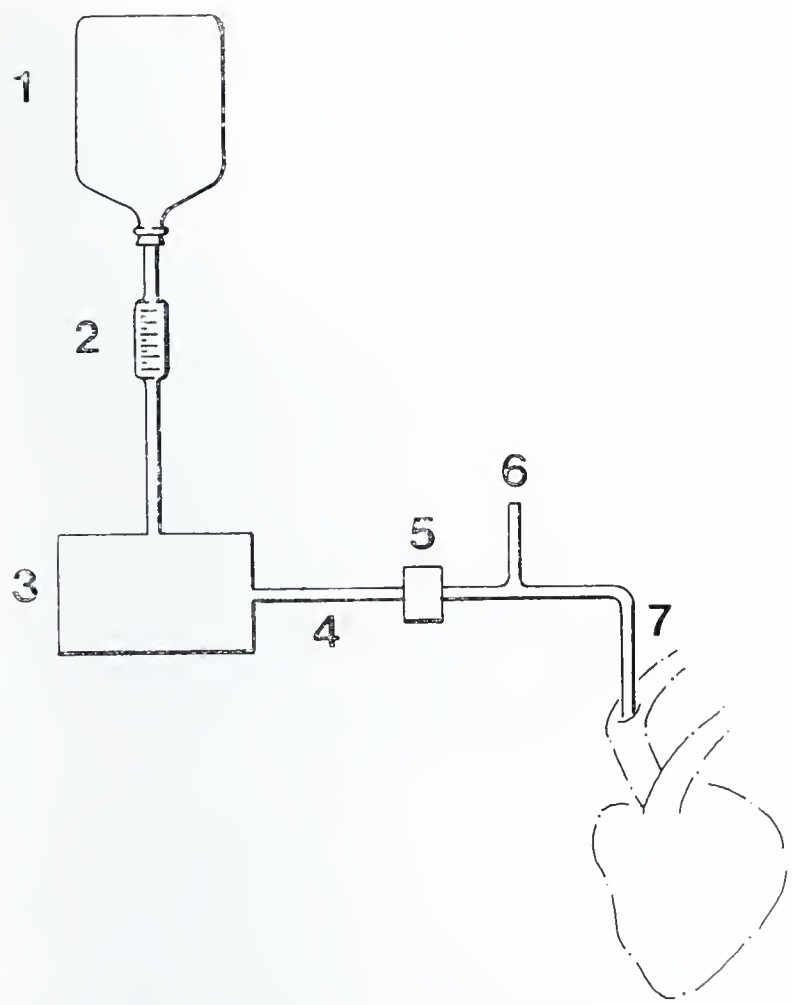

FIGURE 4: IVH apparatus: 1) amino acid-glucose infusate; 2) calibrated burette; 3) constant infusion pump; 4) disposable tubing which adapts to pump head; 5) Millipore filter; 6) T-connector for other IV infusions; 7) radiopaque superior vena cava catheter.

protein to repair deficits, and to maintain stores. Adequate minerals are added to complete the mixture. Glucose provides the main source of calories and Dudrick suggests that maximal benefit is to be gained by administering up to 5 litres of these solutions per 24 hours (calorically this is clearly "hyperalimentation").

TABLE 1
HYPERALIMENTATION SOLUTION

CONSTITUENT	CONTENT
Volume	900cc./bottle
dextrose	225 gm.
casein hydrolysate	25 gm.
sodium	17.5 meq.
potassium	9.5 meq.
calcium	2.5 meq.
magnesium	1.0 meq.
chloride	10.0 meq.
phosphate	15.0 meq.
calories	1000
pH	5.1

Current hyperalimentation in use at the Mayo Clinic, Rochester, Minnesota. A daily vitamin supplement is added to this solution, and electrolytes are added as required[18].

Conspicuous by its absence from the first infusion is the lipid component. Although American workers in the early 1960's had developed a lipid solution from cotton seed oil, many difficulties were experienced clinically, especially with allergic reactions[19]. As a result all intravenous lipids were withdrawn from the American market.

Workers elsewhere — notably Scandinavia — have developed an alternate infusion which contains a lipid component based on soybean oil which is well tolerated in man.[19] This infusion would appear to provide a more physiological diet. This type of infusion is advantageous for other reasons. Fat has a high caloric value and furthermore emulsified fat exerts no osmotic pressure. By the use of fat emulsions a large amount of calories can be supplied in a small volume of fluid without the drawbacks inherent in hypertonic solutions of amino acids and carbohydrate alone. It is in fact conceivable that long term alimentation using a balanced mixture of protein, carbohydrate and fat may soon be carried out through a peripheral vein. Table 2 outlines the composition of Intralipid®, the current fat emulsion used at the Toronto General Hospital (TGH). In Canada both types of solutions are currently in use, and both types have shown promising results[8, 19].

TABLE 2
INTRALIPID 20%

CONSTITUENT	CONTENT
volume	1000 cc.
fractionated soybean oil	200 gm.
lecithin (egg yolk)	12 gm.
glycerol	25 gm.
sterile water to	1000 cc.
calories	2000 (approx.)

Composition of current lipid infusion currently in use at the Toronto General Hospital. This solution is used in conjunction with amino acid-protein infusion in 5% dextrose and water. This information was obtained from package insert. Vitamins and electrolytes are added to this infusion.

Of extreme importance is the maintenance of a suitable electrolyte environment in patients receiving all their nutrients by vein. Small amounts of electrolytes are available in the standard solutions. For proper utilization of protein, potassium, phosphorus and perhaps magnesium mus tbe available[18]. The losses of electrolytes will vary depending on the patient; however by monitoring serum electrolytes, replacements can be added to the infusion as required. Some centres[9] suggest bi-weekly administration of plasma (10 cc./kg.) to provide trace elements and fatty acids not present in the mixture. Iron requirements may be maintained by weekly intramuscular injections of iron dextran. One should also make certain to supply calcium, magnesium, and other trace metals as these are often neglected by those ordering infusions.

Once patients have stabilized to their feeding programmes certain parameters are monitored to ensure that they are in control. Daily weight, fluid balance, urine specific gravity, urine sugars and acetone are usually obtained. Serum electrolytes and osmolarity are monitored tri-weekly. After an initial assessment of the BUN,

blood sugar and serum triglycerides weekly sampling may be sufficient.

APPLICATIONS

The list of applications to which this technique may prove of benefit is far from complete. The discussion below offers a partial list. A useful approach to the problem of application is to consider conditions where it is desirable to put the entire gastrointestinal tract at rest for a period of time. Included here would be congenital defects of the abdominal wall, intestinal and pancreatic fistulae and inflammatory disease of the bowel. A second group of conditions are those where the bowel is not available for alimentation by the usual route. These would include short bowel syndromes and obstructive lesions such as carcinoma of the pancreas. A third group are those conditions where the alimentary tract is essentially normal but metabolic problems or anorexia inhibit the use of oral alimentation. Here one might think of patients with renal or hepatic failure as well as those who are anorectic secondary to burns or cancer chemotherapy. As most of the current literature refers to IVH the discussion which follows refers primarily to that technique.

1) *Pediatric conditions*

Any infant whose life is threatened because feeding via the gastrointestinal tract is impossible, inadequate or hazardous should be considered as a candidate for IVH. The goals of therapy relate directly to the underlying condition. In chronic non-specific diarrhea prolonged bowel rest is curative. Dudrick reports a more dramatic example[8]. A newborn infant had a ruptured omphalocoele which could not be entirely reduced into the abdomen. A sterile envelope was created to contain and protect the extraperitoneal bowel by suturing a siliconized rubber impregnated mesh to the fascia. IVH was started and the infant gained weight while the bowel remained at secretory and mechanical rest. With time the inflammation and edema of the empty bowel subsided, and the abdominal cavity grew to accommodate it. Reduction was achieved and the silastic mesh excised. The abdominal fascia and skin subsequently healed and the infant commenced to eat, grow and develop normally.

Premature infants will often regurgitate feedings despite apparently normal gastrointestinal tracts. Until a mature bowel has developed IVH offers a method of providing calories for basal requirements and growth[9].

2) *Inflammatory disease*

This group includes ulcerative colitis, regional enteritis and granulomatous colitis. The results of treatment with IVH in these patients has been very encouraging. Dudrick reports several cases of remissions in patients with granulomatous disease of the bowel once started on IVH. Clinically decreased abdominal pain, decreased anorexia, nausea and vomiting have all been noted. Some patients have shown improvement of their gastrointestinal tracts on x-ray with resolution of inflammatory masses. Weight gain, increased strength and fistula closure has occurred in these patients while on IVH. Those patients undergoing surgery have had pre-operative reversal of their catabolic state via their improved nutritional status and were much better surgical risks.

3) *Short-bowel syndromes*

In patients with large bowel resections (e.g. post-trauma or post-infarct) IVH has proved extremely valuable. For, providing the patient can survive long enough, the remaining segment of bowel shows an amazing adaptive ability. This adaption occurs via hypertrophy of the remaining segment so that its absorptive surface is markedly increased[1,12]. During adaption both types of nutrition are required. Eventually some patients will reach the stage where adequate nutrition can be maintained completely orally. The value of IVH to these patients is that it allows them time for adaption — an element which could not be provided in the past.

4) *Catabolic states*

In 1932 Cuthbertson first described the catabolic phase occurring post-trauma or post-surgery[3]. Until recently it was felt that this response was obligatory. IVH however has provided positive nitrogen balance even in these hypermetabolic states[8]. In the normal patient this is of little consequence, but in the malnourished one the risk of infection and other post-operative complications can be decreased[19].

5) *Surgical complications*

IVH has been used in the treatment of chronic intestinal obstruction due to adhesions[9]. In these cases restoration of adequate nutrition will permit corrective surgery. Dudrick[8] has reported the healing of a leaking anastomosis in a 62-year-old patient following esophagogastrectomy after being maintained on IVH for a month. He has similarly reported great reduction in exocrine pancreas secretion in patients with pancreatic fistulae. By putting the bowel to rest, wound healing and fistula closure has occurred in this group.

6) *Renal failure*

The basic hyperalimentation solution is modified in patients with renal failure. Protein is normally supplied by fibrin or casein hydrolysates which contains large amounts of non-essential nitrogen. In uremic patients a modified intravenous Giovanetti diet is employed. This consists of infusing an essential amino acid solution together with hypertonic glucose. By supplying adequate calories in the presence of the minimal requirement of the eight essential L-amino acids, urea nitrogen can contribute to protein synthesis[7]. BUN values of patients on this regime have fallen and balance studies indicate continued protein synthesis. The clinical picture of azotemia — nausea, vomiting, mental confusion, muscle twitching and body wasting has been reversed.

This technique is of particular value in patients with symptomatic uremic gastroenteropathy or the patient

with severe abdominal injury complicated by renal failure. In the chronic renal failure patient this high calorie select amino acid diet can reduce the frequency of dialysis. The problem of sodium, potassium and phosphate excess can be overcome by reducing intake to match extrarenal losses[12]. One week between dialysis treatment appears to be the maximal duration since the reduced frequency of dialysis has invariably led to the development of serious peripheral neuropathy. Thus, any prolonged attempt to reduce the total amount of dialysis must be carefully monitored by serial measurement of nerve conduction velocities.

7) *Liver disease*

In patients with severe liver disease high levels of ammonia accumulate in the blood due to the liver's compromised nitrogen metabolism. In these patients adequate enteric feeding is difficult. Dudrick[8] studying 10 patients with varying degrees of hepatic encephalopathy and malnutrition, reported that blood ammonia levels are significantly reduced when adequate calories are provided with hypertonic glucose and nitrogen of high biological value via L-amino acid infusion.

8) *Conditions of anorexia*

Included in this group are those patients being treated for malignancy. Many of these patients who receive radiation or chemotherapy may require reduced dosages because of anorexia, nausea and vomiting resulting from therapy. IVH while on anti-neoplastic therapy will reduce this morbidity and should provide a method of delivering more effective treatment since therapeutic doasge may be prolonged.

COMPLICATIONS

Although the technique of total parenteral feeding is relatively new, several complications have already become apparent. Infection and dextrose intolerance have provided the major complications while others have occurred less frequently.

1) *Infection*

Infection with a wide variety of organisms occurs and some ordinarily non-pathogenic organisms such as *Candida albicans* become major problems.[9, 10, 13] *Candida* gains entry from the skin along the catheter tract or via contaminated intravenous solutions. The catheter, acting as a foreign body in the blood, may perpetuate the growth of organisms entering at distant sites. Sepsis may be minimized if the following precautions are observed:

1) aseptic preparation of infusate;
2) tunneling of catheter subcutaneously 2 to 4 inches between skin and vein entry site;
3) meticulous skin care about catheter entry site with frequency dressing changes, use of bactericidal and fungicidal ointments;
4) avoidance of blood sampling from venous line or unnecessary disconnecting.

Presence of fever, weight loss, or failure to gain weight are all clinical clues to underlying sepsis. *Candida* septicemia is initially treated only by removal of the central catheter. If positive blood cultures persist the following day the appropriate agent should be given. Examples of which have been isolated are: *Staphlococcus epidermidis*, *staphlococcus aureus*, *pseudomonas aeruginosa*, α-hemolytic *streptococcus* and group D *streptococcus*.[10]

2) *Dextrose intolerance*

Tolerance to large infusions varies widely from patient to patient and from time to time in the same patient. This intolerance which may occur initially or later on in treatment manifests itself as hyperglycemia from failure of insulinogenic reserve of the pancreas. This phenomenon should be watched for by monitoring urinary glucose. It has been suggested that the patient at no time spill greater than 1% glucose[12]. If higher levels are observed dextrose infusion should be decreased, or insulin should be added to the infusion. If these precautions are not observed osmotic diuresis and serious dehydration may otherwise occur. Sudden cessation of dextrose infusions may potentiate an insulin reaction. For this reason when treatment is being discontinued dextrose infusions should be gradually reduced.

3) *Fluid and electrolyte balance*

Certain authors recommend the utilization of two-channel infusion systems for patients receiving total parenteral feeding. By using this apparatus electrolyte problems may be managed separately from constant nutrient infusion[12]. Careful monitoring of serum potassium is especially important in the severely depleted patient started on IVH. With improved nutrition and anabolism large amounts of extracellular potassium shifts into the cells. In the face of normal obligatory losses of potassium in the urine of the post-operative patient, it is clear that potassium requirements will often exceed the usual 40-60 meq. generally given per day. Further increased intake of potassium is essential to achieve weight gain and protein synthesis[6].

4) *Other complications*

Depression and other psychological problems have often developed in patients undergoing long-term renal dialysis. Hopefully these types of reactions stemming from chronic connection to a machine will be offset in the IVH patient by a marked improvement in physical health.

Certain technical difficulties such as pneumothorax formation, accidental withdrawal of the catheter from the superior vena cava, or perforation of the vena cava by the catheter are rare at present. Their incidence should further decrease as familiarity with the technique occurs.

Excessive aminoaciduria may rarely occur in very small infants or in older patients with abnormal renal function. Patients on long term IVH may run the risk of developing subtle deficiency syndromes. These may result from the absence of certain trace metals or perhaps from

the lack of essential but as yet unidentified nutrients produced by the bacterial flora of the bowel[12].

SUMMARY

Hypertonic nutrient solutions infused continuously into the superior vena cavas of patients with a wide variety of disease is a relatively new technique. The method has conclusively shown its ability to promote infant growth and restore weight loss in adults. As a new technique changes and modifications will occur as improved methods become available. The purpose of this article was to introduce this subject to the student and allow him to watch the technique develop during his later medical career. In conclusion I quote from Dr. Dudrick:

"With judicious application of the technique as a clinical, laboratory investigative, and therapeutic tool, the new horizons for intravenous therapy will continue to expand — extending to practically every medical specialty and into many areas of basic research. As relatively few of the potential uses have been explored to date the new horizons for intravenous therapy are real and exciting and appear to be limited only by the ingenuity and ambition of man."

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Colorectal Adenocarcinoma

Paul Adam, Meds 7T2

INTRODUCTION

Adenocarcinoma of the gastrointestinal tract is still a major medical problem. The American Cancer Society estimated that in the United States in 1968, 75,000 new cases would manifest and 45,000 patients would succumb to their disease. It is a tumour whose numbers are large, yet its management has changed little over the last century. In fact, if allowance is made for improvement in immediate post-operative mortality (due to better anesthetic technique, antibacterial chemotherapy and hemostasis), the five-year survival for this tumour is essentially unchanged over the last forty years.[1]

It is the purpose of this paper to present a brief review of the conventional approach to colorectal carcinoma in terms of incidence, pre-malignant lesions, symptomatology and treatment. Subsequently, a further concept, developed from the investigation of immunological aspects of neoplasia and its possible clinical applications will be discussed.

INCIDENCE

The number of cases of colorectal adenocarcinoma expected in the United States in 1968 has been mentioned. Figures for Canada may be approximated by assuming that our population is about 10% of the United States. Table I shows that carcinoma of the intestine and rectum has the second highest incidence and the highest mortality of all tumours reported to the DBS in 1969.[2]

TABLE I

New Primary Sites of Malignant Neoplasms in Canada (1969)

SITE OF TUMOUR	INCIDENCE/ 100,000	MORTALITY/ 100,000
Skin	47.0	1.7
Intestine & Rectum	32.8	22.4
Breast	30.6	13.2
Trachea, Bronchus & Lung	22.9	22.3
Prostate	16.9	14.8
Stomach	12.9	12.3
Larynx	3.7	1.0

Cutler and Shimkin[3] in a different approach to the epidemiology of this disease have shown that 1.3% of males and 1% of females will develop colorectal carcinoma at one point in their lives. The importance of this tumour as a major health problem is unquestionable.

PREMALIGNANT LESIONS

This name is a misnomer since it implies a pathogenetic relationship which to date has only been shown to be a statistical one. The significance of these lesions in the etiology of malignant disease of bowel is unsettled.

a) *Polypoid adenoma*

This is the most common tumour of the colon and rectum. Rider's[4] series of sigmoidoscopically investigated patients puts the incidence at 5.1% of the average population. Usually, they are asymptomatic but may present with bleeding, disturbed bowel function or abdominal pain. Their relationship to carcinoma is at present a contentious issue, but it has been shown that the risk of developing cancer of the colon in these individuals is greater than the general population. The question at issue is whether these lesions themselves develop into cancer or whether the colon which harbors them has more potential to become neoplastic. It is generally agreed that if possible, they should be removed because their biologic potential is unknown and absolute diagnosis can only be confirmed by pathologic examination.

b) *Familial Polyposis of Colon*

This is the most clearly pre-malignant condition known in clinical medicine. It is a mendelian dominant disease with 80% penetrance. Polyps usually appear at puberty and are numerous, being both sessile and pedunculated. With no treatment, 100% of cases will develop into carcinoma. Total colectomy and ileostomy is the treatment of choice, however, some authors propose subtotal colectomy with ileorectal anastomosis. This latter course requires faithful sigmoidoscopic follow-up and fulgerization of recurring polyps, but risks the development of rectal carcinoma.

c) *Gardner Syndrome*

This mendelian dominant condition consists of the association of soft-tissue tumours, bone tumours and multiple colonic polyposis. The polyps require just as cautious observation as those of familial polyposis and their surgical removal is the treatment of choice.

d) *Villous Tumours*

These comprise only 2-5% of all colorectal polyps but are potentially more dangerous than the commoner adenomatous polyps. They are usually seen in the elderly, are found in the caecum or rectum and present with rectal bleeding, diarrhea, mucorrhea or protrusion. Rarely, these lesions may be of the hypersecreting type and may be the source of fluid and electrolyte loss (in particular K^+). By far the most important consideration though, is their malignant potential and it is for this reason that if possible these lesions should be resected.

e) *Ulcerative Colitis*

Patients with ulcerative colitis have an eight-fold incidence of cancer of the colon as compared with the average population. Moreover, their tumours usually begin at an earlier age, are more likely to be multiple, are more poorly differentiated and are difficult to diagnose because the symptoms of ulcerative colitis may be indistinguishable from those of the carcinoma. For these reasons, many surgeons recommend prophylactic colectomy for those patients who have had severe pancolitis for longer than ten years and whose onset was prior to age eighteen.

SIGNS AND SYMPTOMS

In order to appreciate the ways colorectal tumours may present, it is of value to distinguish between the left and right colon in terms of anatomy and nature of the lesion.

	RIGHT COLON	LEFT COLON
BLOOD SUPPLY	Superior mesenteric artery via right colic and middle colic	Inferior mesenteric artery via left colic, sigmoid and superior hemorrhoidal arteries
CONTENTS	Liquid	Solid
LESION	Bulky fungating lesion projecting into lumen	Annular lesion causing constriction of lumen
PRESENTATION	Bleeding (usually occult), anemia, weakness, RLQ mass	Change bowel habit, pencil stools, diarrhoea, occasionally perforation

Both may present with weight loss and abdominal pain.

SPREAD

This is the most important clinical aspect of this tumour at the time of diagnosis since this is the factor which will determine the fate of the affected individual. A quick review of the types of spread and some comments about them are in order.

a) *Venous*

—This may occur at time of resection; therefore early ligation of pedicles and minimal handling of tumour are suggested.

—Spread via portal system, therefore hepatic secondaries are very common.

b) *Lymphatic*

—Comments above apply here too.

—Moreover, it must be remembered that depending on the site of the lesion, spread may be via pelvic and/or abdominal lymphatics.

c) *Intramural*

—An adequate margin must be excised. This is especially difficult in lesions around the rectosigmoid junction where the surgeon is trying to avoid colostomy by doing an anterior resection.

d) *Direct Extension*

—To abdominal wall, adjacent organs, e.g. stomach, duodenum, bladder and in males to prostate.

e) *Transperitoneal Spread*

—This usually implies inoperability.

f) *Implantation along lines of Anastomosis*

—This important cause of recurrence[5] can be minimized by early isolation, minimal handling and by chemical irrigation of the ends to be anatomosed.

PROGNOSIS

There are basically two classifications which relate the characteristics of the tumour to survival.

The first is Bröder's which is a histologic classification relating the grade of malignancy to survival. In general a higher grade of malignancy is associated with decreased survival. However, this classification is difficult to apply because of the inability to standardize the histologic criteria of degree of differentiation of the malignant cells.

The second classification is Dukes' and is based on anatomical spread of the tumour. It has been found to correlate quite well with the subsequent fate of the patient and as a result has been used by many as a prognostic sign.

TABLE II[6]

5-Year survival of surgically treated Colorectal CA using Duke's classification.

	5-YEAR SURVIVAL
Stage A.—Involving Bowel Wall only	95%
Stage B.—Outside Wall, but not to Regional Lymph Nodes	77%
Stage C.—Involvement of Regional Lymph Nodes	33%

CONVENTIONAL THERAPY

The treatment of colorectal adenocarcinoma falls into the three broad categories of surgery, chemotherapy and radiation.

a) *Surgery*

This is the treatment of choice and the object is to remove the tumour entirely. Naturally the task is much easier if the lesion is well circumscribed and is next to impossible once metastasis has occurred. The details of surgical ablation are beyond the scope of this paper, but some principles stand out:

(i) Early diagnosis and early surgical intervention are still the best therapeutic measures possible.

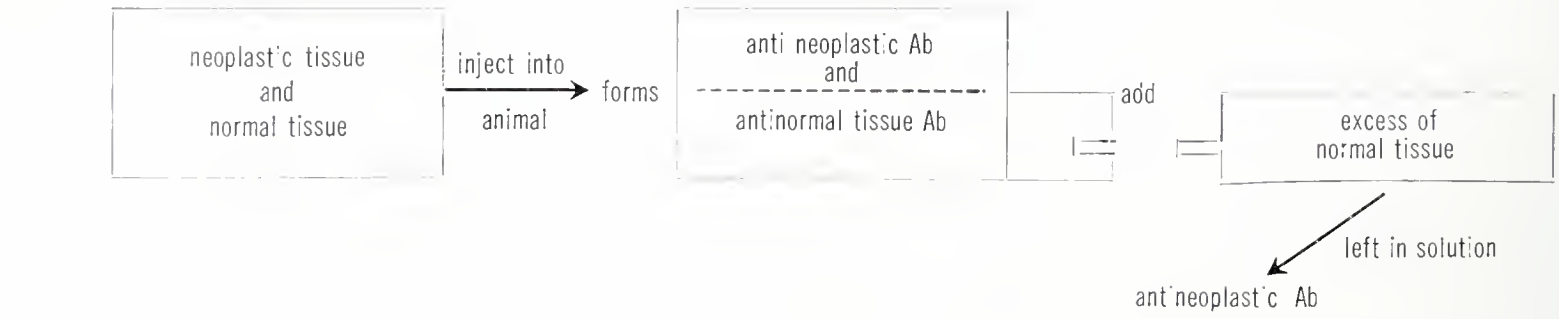
(ii) Early ligation of lympho-vascular pedicles with minimal handling of bowel is essential.

(iii) Wide excision of bowel wall with corresponding dissection of regional lymph nodes can increase cure rate, or at least delay recurrence.

(iv) In selected cases it has been shown that hepatic lobectomy of metastatic lesions has prolonged survival[7] and metastasis to liver should not be cause for cessation of efforts.

b) *Chemotherapy*

The results of this form of treatment have been inconclusive. Attempts at intravenous injection, intraperitoneal lavage, regional perfusion and intra-luminal administration of 5-FU, and other agents have been tried. There is a continuing search for the development of more specific drugs. To date though, only the use of agents to reduce recurrence at lines of anastomosis has been definitely shown to be of value.



c) *Radiation*

The use of radiation has been limited for two main reasons. Firstly, primary adenocarcinoma of the bowel does not respond to radiation at doses which do not at the same time destroy normal tissue (although this is not true for metastases). Secondly, pre-operative radiation makes subsequent surgery more difficult. As a result, radiation has been used only in patients who refuse operation, or in those in whom operative risk is too great.

IMMUNOLOGICAL APPROACH

(i) *Humoral Mediated*

For well over half a century, it has been the goal of cancer immunologists to apply immunologic technics to the study of neoplasia. This had met with little success until Foley[8] in 1953 demonstrated specific antigenicity in a class of experimental animal tumours. In 1965, Gold[9] demonstrated by both absorption and tolerance techniques, the existence of antibody specific to tumour tissue of the GI tract.

This technique involves the sensitization of rabbits to both neoplastic and normal tissue. The addition of an excess of normal tissue antigen to the serum, thus produced, results in the removal of antibody to the normal tissue and leaves in solution only the antineoplastic antibody.

This technique takes advantage of the fact that immunologic tolerance is high in neonatal rabbits. Thus, a tolerance to normal tissue antigen is built up so that when subsequent injection of normal tissue antigen and tumour antigen is administered, only antibody to the neoplastic tissue is formed.

Antisera prepared by both technics were found to be very similar in content and quality of antibody. Moreover, in the study of over 200 samples of colonic adenocarcinoma, the same tumour-specific component was found in every neoplasm. Numerous studies have excluded the possibility that these antibodies are in response to some material other than the tumour itself. Investigation of other tissues for the presence of the antigen revealed it in the following:

(i) All primary adenocarcinomata arising from digestive system epithelium derived from entoderm.

(ii) All metastatic lesions derived from adenocarcinomas of the digestive system.

(iii) All embryonic and fetal digestive organs between 2-6 months of gestation.

It was because of this latter fact that the antigen involved was named "carcinoembryonic antigen" or "CEA". Interestingly, in those patients whose cancers had metastasized, the serum was negative for the anti-tumour antibodies, and, this component could not be detected in any other normal, diseased, or neoplastic tissue by Gold or his associates. Recent reports have disputed the specificity of CEA but on-going investigation is attempting to clarify this point.

The role of CEA antibody has not yet been determined

and in particular there has been no demonstrated relationship between titre of antibody and course of the disease. Electromicrographic investigation has shown that the CEA is localized to the glycocalyx of the neoplastic cell. Biochemically it is a protein-polysoccharide molecule of sedimentation coefficient 75-85 and an immunoelectrophoretic mobility in the β-globulin range on agar gel which has been found to be quite consistent from one human digestive system to another.[10]

Comparison of tumours induced by carcinogens have shown that their antigenic structures are specific to the individual tumours, yet virus-induced tumours have been found to have universal cross-reactive tumour-specific antigenicity.[11] This latter finding has great import for the possible viral etiology of adenocarcinoma since it has earlier been shown that biochemically CEA is identical from one human digestive system to another. This is at present a major question in many neoplasms, and information from this specific tumour may be applied to neoplasia in general.

Recently a radio-immunoassay technique for the detection of CEA has been developed. If detectable levels are encountered, it is suggestive of GI tract carcinoma. Clinical trials are now being carried out to investigate the possible use of this test as a mass screening technique for the detection of GI carcinoma.

(ii) *Cell Mediated*

Another prong of the immunologic attack has been the investigation of cell-mediated immunity. This has largely been pioneered by the work of the Hellströms in Seattle who developed the "colony inhibition technique"[12] Basically, this consists of the inhibition of growth of plated CA cells by the application of various agents. They found that:[13]

(i) in 51 of 59 (86%) patients with adenocarcinoma, their own lymphocytes had a detrimental effect on the plated tumour cells.

(ii) 78 of 87 (89%) had a similar effect on different human tumour cells but of the same histological type as those of the lymphocyte donors.

Similar information was obtained for other plated tumours, e.g. malignant melanoma, breast, testis, endometrium, ovary and various sarcomas. It was significant that lymphocytes from patients with adenocarcinoma of GI tract not only inhibited plated tumour cells but also inhibited the growth of fetal gut and liver cells.[14] This suggests that anti-CEA antibody and the cell-mediated lymphocyte response are to the same antigen — namely CEA. Although this latter suggestion has not been proven, it is significant to note that the incubation of peripheral blood lymphocytes from patients with digestive system cancer in the presence of CEA failed to stimulate a significant degree of lymphocyte transformation, as measured by H^{3+} thymidine uptake into DNA[15].

Speculation has been that CEA is a product of so-called "genetic de-repression"[16, 17]. The theory states that during development totipotential cells become restricted in their repertoire of genetic expression by the action of "repressor genes". During carcinogenesis "depressive-differentiation" leads to the expression of those genes which had been previously blocked by the repressor genes. Thus, there is renewed formation of material which had been produced in fetal life prior to differentiation.

No matter what the status of the theory, it is clear that the discovery of CEA has revolutionized the thinking of scientists on the etiology and nature of carcinogenesis of GI tract in particular and of all tissues in general. What this will mean in terms of prophylaxis and/or treatment remains to be seen but it is certain that a new area for future investigation has been opened.

SUMMARY

Carcinoma of the GI tract remains to-day a disease whose treatment and prognosis has changed little since the development of modern surgical techniques. It has been shown to be a common condition whose exact etiology and pathogenesis have not yet been fully understood. Recent discoveries in the field of immunology as applied to neoplasia have shown promise in at least the detection of this type of tumour. Whether further applications will accrue is the question that present investigators have addressed themselves to. In any case, the tempo of research in this area has quickened, and answers to questions regarding the basic process of carcinogenesis are being sought. The model of carcinogenesis in gut has served as a stimulus for parallel efforts in the investigation of the etiology and pathogenesis of other types of neoplasia.

ACKNOWLEDGEMENT

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(Continued on page 79)

Aerophagia Or Gastric Gas Tricks

Joseph Tokaruk, 7T2

Belching, bloating, and flatus expulsion all seem to prove the dictum that to air is human. Aerophagia or air swallowing is a normal, unconscious, physiologic process that when exaggerated gives rise to various symptom complexes, even though it is itself not a symptom. By far, air swallowing produces the most common functional disorders encountered in gastroenterology. Considering that approximately 75% of patients seen by the gastroenterologist have a functional disorder either alone or in association with organic disease[1] we can't help but come to the conclusion that a lot of people are "full of hot air."

The importance of gas syndromes cannot be too great for the physician, surgeon and even the one tract-minded gastroenterologist. Superimposed gas syndromes may mask less intense symptoms of serious diseases such as cholelithiasis, peptic ulcer and angina pectoris, be mistaken for serious diseases themselves or serve as a nuisance to the patient at the most embarassing times. Excuse me.

Normal Gas Physiology

Babies start swallowing air a few minutes after being born. Within hours of birth a fine balance is achieved and the amount of gas in the gastrointestinal tract becomes relatively fixed.

Gas in the gut may be of exogenous or endogenous origin. Exogenous gas is unavoidably swallowed during eating and drinking. Normally, closure of the superior esophageal constrictor prevents air from entering the esophagus. Seventy per cent of the total gas is swallowed air. The rest or endogenous gas is made up of that which diffuses from the blood stream (20%) and that which comes from bacterial decomposition of food residues (7-10%).

Depending on its location in the G.I. tract gas varies both in volume and composition. In the stomach there is usually a static volume that can be seen on a routine chest film. Most gastric gas is swallowed air but analysis of aspirated gas from early morning fasting stomachs shows the composition to be: 0_2-15%, CO_2 – 4-8% and the rest nitrogen.[2] This observation implies that swallowed air is altered by partial absorption into mucosal blood vessels and diffusion of blood gases out of the same. Furthermore, the astute reader will be happy to learn that given the above concentrations of the gases, mankind isn't really full of hot air.

The small bowel normally contains no gas, but when obstruction occurs it rapidly fills up with gas proximal to the obstructed part.

Gas is always present in the normal colon and in fact there is a rapid turnover. Air introduced into the stomach may pass through the small intestine to the cecum in about ten minutes and the result in the passage of flatus in about thirty minutes.[3,4] The average amount of flatus expelled per day is about 500cc.[5] This means that in Canada alone approximately eleven million litres of flatus enter the atmosphere every day. Extrapolating, we would hastily conclude that China should contribute more than any other nation to the world's flatus resources. But no doubt the astute reader having eaten beans knows that flatus production depends greatly on diet. In fact so much so that he who lives on beans alone, lives alone. Diets high in cellulose or inadequately cooked starch which is unaffected by human digestive enzymes provide substrate which is attacked by bacteria in the colon, a bacterial Eden, and converted into excess CO_2 and methane. Cabbage, cauliflower, navy beans, radishes and cucumbers are all gaseous vegetables. Knowing these facts we can say that the answer to the question as to which country produces the most flatus is still up in the air. It remains for some gastroenterologically orientated, unbiased comparative anthropologist to solve in the future.

Table 1 summarizes some little known facts about flatus.

Table 1
IMPORTANT FACTS ON FLATUS

1. Has been around since ancient times.
2. Average amount passed per rectum at one time 40-300cc's depending on the muffler qualities of the rectum.
3. World record for amount passed at one sitting claimed to be held by the Russians — see "Proceedings of the Geneva Disarmament Negotiations", B. Borborygmik.

Specific Syndromes

Now that the normal physiology of gas in the gastrointestinal tract has been described we can consider the aerophagic syndromes. Table 2 gives a classification which is certainly not conclusive and is by no means intended, like most classifications, to scare the reader.

Table 2
SPECIFIC AEROPHAGIC SYNDROMES

I *NEUROTIC EXHIBITIONALISTS (Gas tricksters)*
- A) Esophageal-Belcher.
- B) Rectal-Exhauster.

II *MAGENBLASE SYNDROMES*
- A) Early postprandial fullness, pressure, bloating.
- B) Pseudoangina.
- C) Acute gastric dilatation.

III *COLON GAS SYNDROMES*
- A) Cecal.
- B) Hepatic flexure.
- C) Splenic flexure.

I *NEUROTIC EXHIBITIONALISTS*

Esophageal-Belcher

Beginning with the esophageal belcher, we see in him an individual who eructates on *burpose*, by gulping air then at the critical moment, just before it reaches his stomach he lets go his esopha*gas*. He can be found at political meetings, after lunch hour biochemistry lectures and ethnic weddings.

Rectal-Exhauster

The Rectal-Exhauster, certainly a more skilled individual simply because of the biomechanics involved is definitely a less liked creature than the Esophageal-Belcher. Euphemistically referred to as "he's the one", this neurotic person delights in breaking the unwritten social law that rectal silence is golden. This he does to seek attention. Needless to say males predominate over females but with Women's Lib rising, I predict that the gap will be narrowed as women become more aggressive. Some authorities emphatically claim that there are no female Rectal-Exhausters, but Siverge[6], having studied 500 nurses, claims that the characteristic is not X linked. No doubt, Freud aired his views on the subject, but I was unable to find references. However the title of one of Bach's works "Air on a G string" would seem to agree with Siverge's point of view.

II *MAGENBLASE SYNDROMES*

Early Post-Prandial Fullness

The magenblase syndromes are caused by an enlarged gastric air bubble. Symptoms such as postprandial epigastric fullness and pressure or bloating relieved by eructation of air make up a typical presentation of the commonest of the magenblase syndromes. As the day goes on the patient swallows more and more air. Even though some may be eructated and some escapes through the pylorus, the gastric air bubble gradually increases in size. Men coming home from work may have to loosen their belts. Usually the greatest distress comes after the evening meal when the North American apartment dwelling caveman triumphant after an eight-hour hunt interrupted by lunch and two coffee breaks sits down to eat and eat. Unfortunately before getting too far he begins to feel sensations of fullness, bloating and pressure in the epigastrium. The first reaction is to blame everything on the wife's cooking, claiming that it causes too much gas. However the gas was present in the stomach before the meal began. All that the food did was to increase the pressure in the stomach just enough so that symptoms resulted. The wife had nothing to do with it.

It must be emphasized that the occurrence of the symptoms does not depend on the amount of air in the stomach or the amount of food eaten but rather on the tonicity of the stomach and the state of tension in the individual. That is why symptoms come on most often after the patient eats too quickly to allow the stomach to adaptively relax to hold its increased content. Similarly the overlying abdominal muscles fail to relax (von Mering reflex) to accommodate the increased abdominal content. For most, relief is just a belch away since eructation of air lowers intragastric pressure and relaxes the stretch upon the stomach wall.

Pseudoangina

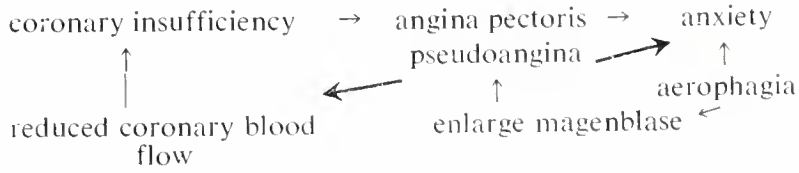
This is a perplexing variant of the magenblase syndrome that manifests itself as sharp stabbing pain in the left rib margin extending at times to the left pectoral region. Characteristically the pain comes on after a huge meal and is relieved by a belch. Sometimes accompanying shortness of breath, palpitations or a sense of suffocation can cause the patient and physician to confuse pseudoangina with true angina. An important differentiating factor is the location of the distress which in true angina is substernal but in pseudoangina is to the left of the midline.

To complicate matters both pseudoangina and angina may co-exist. Anxiety provoked by angina may lead to excessive air swallowing which forms a large magenblase that has been postulated to reduce coronary blood flow by the following mechanisms:

1. Increased blood flow to digestive tract therefore decreasing coronary flow.
2. Pseudoanginoid pain causing epinephrine release which increases the work of the heart.
3. Greatly distended stomach may press on the inferior vena cava decreasing venous blood flow.

Table 3 summarizes how anxiety aerophagia angina and pseudoangina are interrelated.

Table 3 (Bockus)



It is important that the physician discuss with the angina patient how aerophagia can aggravate his angina.

Acute Gastric Dilatation

Any discussion of aerophagia must include acute dilatation of the stomach which is defined as rapid enlargement of the stomach and duodenum occurring most often postoperatively. Most frequently on the second or third day after a wide variety of abdominal and pelvic operations a gradual onset of listlessness and apathy can be seen in the patient. Soon anorexia and nausea begin, followed by vomiting of greenish material. Seldom is there much pain. On examination there is asymmetrical distention of the abdomen in the left hypochondrium. A succussion splash and a uniformly tympanic note over the distended part may also be present. Peter's sign, the hearing of the heart beat over a stomach filled with gas, is helpful in making the diagnosis.

A postulated mechanism to account for the rapid filling up of the stomach with air and secretions proposes that the third part of the duodenum is compressed by the superior mesenteric vessels. Excessive air swallowing occurs as a result of anxiety or is stimulated by dryness of the mouth postoperatively due to medication or dehydration. The stomach becomes greatly dilated almost filling the entire abdomen. There is danger if ischemic necrosis, gastric perforation, serious compromise of respiratory volume or electrolyte disturbance from the associated vomiting.

Treatment consists of passing a nasogastric tube and evacuating the contents of the stomach.

III *COLON GAS SYNDROMES*

There may be a tendency to confuse irritable colon gas syndromes. Both occur in people of much the same emotional makeup, i.e. depressed, cynical, hostile but the major physiological difference is that in the gas syndromes colon transport is normal while it is not so in irritable colon syndrome. Furthermore one must remember that the problem in all these syndromes as well as all other aerophagic syndromes is not excessive gas but retention of gas.

Cecal

The cecal gas syndrome presents itself as a steady aching fullness well localized to the right anterior lower abdominal quadrant that can radiate laterally toward the right flank. The usual pattern consists of chronic fluctuating discomfort rarely interrupted by acute severe episodes of pain. Pressure over the cecum produces discomfort therefore loosening any constricting devices such as a belt or girdle brings relief. Sometimes relief may also be obtained by massaging the cecum which apparently moves the gas along.

Hepatic Flexure

The hepatic flexure syndrome is often confused with gall bladder disease. In some patients gas trapped in the hepatic flexure is described as a pressure or fullness felt intermittently in the right hypochondrium. Radiation may occur to the right shoulder and mid-back. The pain may also be described as a broad stripe across the right chest below the breast. There may be unproductive attempts at belching. When the pain is severe, the patient will restlessly change position in an effort to find relief. Since the patient feels best on an empty stomach, he may be discouraged from eating. (Since the existence of both the cecal and hepatic flexure syndromes it's doubted.)

Splenic Flexure

By far the commonest occuring colon gas syndrome is the splenic flexure syndrome. With the splenic flexure high under the diaphragm fixed by a peritoneal fold, a traplike mechanism is created by the sagging transverse colon and the heavy descending colon. These two cause an angle to form at the peritoneal fold. Gas accumulates in the splenic flexure and if a certain tension in the colon wall is exceeded symptoms will result.

Evidence that distension of the splenic flexure may produce symptoms includes:

i) X-ray evidence of gas in the splenic flexure when symptoms are present and no gas in asymptomatic periods;

ii) reproduction of symptoms by inflating a balloon in the same area.

Between 165-665 cc. of air is sufficient to produce symptoms which consist of distension, pressure or fullness in the left upper abdominal quadrant or precordial area. The pain may be an ache in the left lower chest or pectoral region. There may be accompanying shortness of breath, palpitations, substernal oppression and apprehension, which again suggest angina to the patient and the physician. But, like the pseudoangina of the magenblase syndrome the discomfort is to the left of the midline not midsternal. Anything further compressing the left upper quadrant such as bending or stooping, a large meal, slumping or lying down after a large meal may aggravate symptoms. Some relief is obtained by belching which reduces pressure from a simultaneously enlarged magenblase. Also abdominal massage, the knee chest position or walking about may help the gas to pass through the splenic flexure. The best relief is brought by a bowel movement, enema or flatus expulsion. One must remember that symptoms are frequently precipitated by emotional upsets; resolving the emotional problems that cause the aerophagia will do much to clear up the abdominal complaint.

DIAGNOSIS OF AEROPHAGIA

The diagnosis of aerophagia begins with the history. Complaints of frequent belching, excessive flatus, borborygmi and fullness aggravated by anything constricting the abdomen such as a girdle or a too tightly applied money belt. Similarly stooping, slumping and lying down especially after a large meal make symptoms worse. Paradoxically lying down may relieve the symptoms since with time the abdominal muscles and intestinal musculature relax. Local application of heat also causes relief.

Look for habits such as gum chewing, eating rapidly, excessive use of carbonated beverages (the coca colon syndrome), use of straws, excessive smoking and sucking on candy, all of which may lead to excessive aerophagia. While talking to the patient the astute clinician can detect frequent swallowing, belching and excessive flatus. The patient may be tense, anxious and restless. Sighing is common and may be caused by depression or gas fullness pressing against the diaphragm and interfering with respiration. Try to find out if the patient is undergoing some extremely stressful life situation such as at income tax time.

On examination there may be abdominal distension. Infrequently a visible bulge may be present in the involved colon segment which by palpation may be caused to disappear. There may be tympany in the epigastrium or in the lateral left quadrant. Fluoroscopy may show excessive swallowing of air. X-ray films, to be helpful, should be taken when the patient experiences symptoms. But it must be remembered that symptom production does not depend on the amount of air present but rather on the tension in the gut wall and the tension in the patient.

SUMMARY

Normal gas physiology and the common aerophagic syndromes have been presented. Some practical tips on management have been given but overall treatment has been skillfully avoided. It is hoped the reader doesn't find the concept of aerophagia hard to swallow.

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Case Presentation:

I. Horowitz, 7T2

Crohn's Disease In A Male With Hypogonadotropic Hypogonadism And Anosmia (Kallmann's Syndrome)

The combination of two disease entities, Kallmann's syndrome and Crohn's disease, in a patient is rare. Kallmann's syndrome is characterized by hypogonadotropic hypogonadism, color blindness, synkinesia, anosmia and mental defects;[1] Crohn's disease is characterized by fever, weight loss, anemia, abdominal pain and diarrhea.[2] Kallmann's syndrome may be inherited as an X-linked dominant with incomplete penetrance.[3] Crohn's disease has been related to Jewish origin, people with higher levels of education and aggressive and ambitious persons.[4] The case presented is a non-Jewish male, who has not completed grade school and has a prepubertal mental attitude.

A 31-year-old white Canadian-born male had complained of diarrhea and intermittent crampy abdominal pain for two weeks. At this time he was noted to have hypogonadism. He was treated with tetracycline and belladona and gradually improved over the next two weeks. One month later he was admitted into hospital for investigation of hypogonadism which had been observed in the out-patient department.

The patient was born without any significant complications that he is aware of. He was the eldest of five boys in the family. While his four brothers developed normally, he lagged far behind. His penis remained small; he developed no true masculine facial hair except for a fuzz which he shaved occasionally. His voice remained high-pitched, which he rationalized was due to prior tonsillectomy. He never had trouble with acne. Once in a while he claimed he had a penile erection; but he had never ejaculated. He had never shown any interest in the opposite sex.

The patient had never acquired a sun tan; no matter how hard he tried he would only receive a sun burn. He sweated a lot in the summer. He did not have any salt craving. There was no history to suggest any postural hypotension. He denied any muscle weakness or cramps. There was nothing to suggest either hyper- or hypothyroidism. There was no history of polyuria, nocturia, polydipsia, or polyphagia. He denied any significant headaches or anything to suggest visual field loss. He claimed he couldn't smell flowers, perfumes and food aromas.

All the brothers are taller than the patient (5′ 1″) with heights varying from 5′ 4″ to 6′. All of the brothers are married and some have children. Both parents were a couple of inches taller than the patient.

The patient had an effeminate ebullient manner. He spent his time in hospital drawing pictures of space rockets, cowboys and Indians and cars which had all the characteristics of a ten year old's drawings. He claimed a weight change from 70.5 kg to 47.6 in the past two months. Blood pressure was 130/80 mm Hg with a heart rate of 72 per minute.

He had a peculiar head structure. There were characteristic fine facial creases on the malar, parotid and perioral regions which made him appear much older than his stated age of 31.

There was fine fuzz on his chin. There was definite anosmia (coffee and roses). He did wince at a solution of acetone. The other cranial nerves were normal.

Head, neck and chest examinations were essentially normal. On abdominal examination, there was no tenderness or organomegaly. He had cubitus valgus. There was no hyperextensibility of the joints. The scalp hair felt normal; there was no fronto-temporal hair loss. No axillary or pubic hair was seen. His penile size was prepubertal. The left testis was undescended and measured 1 cm in diameter. Right testis and prostate were absent. He had peri-rectal erythema.

Hemoglobin was 11.4 gm%, white blood cell count was 8,660 with a normal differential. Total iron was 46 μg% with a TIBC of 332 μg% and saturation 14%. Electrolytes and liver function tests were normal. His baseline 17-hydroxycortiscosteroid and 17-ketosteroid levels were normal. An ACTH stimulation test was performed over a three-day period and a brisk response of the 17OH corticosteroids (17.1 mg/24 hours) with some response of the 17 ketosteroids (8.6 mg/24 hours) was observed. Metopirone testing was normal. T-3 resin uptake was 22%, serum thyroxine 5.9 μgm%, 24-hour I^{131} uptake 29.6%; the scan was normal. Urine FSH levels were less than 8 Mouse Uterine Units per 24 hours. An IV Arginine and IV Insulin stimulation tests were normal. Buccal smear was negative for sex chromatin. Karyotyping showed a normal 46XY pattern. Bone age was 15½ years.

The patient's course in hospital was marked by episodes of diarrhea and crampy abdominal pain. Stool cultures and smears were negative. Upper GI and Ba enema were normal. The patient was discharged one month later with the diagnosis of hypogonadotropic hypogonadism with anosmia and diarrhea of unknown etiology. Testosterone therapy was instituted.

During the next six months his gastrointestinal condition became more severe and he was readmitted for complete GI workup.

He had a weight loss of 30 kg in the preceding eight months. He complained of sharp intermittent lower

quadrant abdominal pain which was relieved by bowel movements which he described as loose, watery, occasionally bloody, five to six times per day, very malodorous, light brown, occasionally floating. He had been unable to keep food down, vomiting undigested food and bile about one-half hour after eating. The vomiting was accompanied by nausea and supraorbital headaches. He denied melena.

Pertinent laboratory data revealed a hypochromic anemia of 10.1 gm% Hgb, with no stainable iron stores, an ESR of 56. Fecal fat, xylose tolerance, lactose tolerance and Schilling test were normal. Sigmoidoscopy was normal. Biopsy of a rectal valve at 5 cm showed a mucosal ulcer at the base of which a granuloma with numerous giant cells was found consistent with Crohn's granulomatous colitis. An air contrast barium enema showed ulceration, fissuring and cobblestone appearance from sigmoid to cecum which was deformed and contracted. Upper GI series showed some involvement of the ileocecal valve with dilatation of the terminal ileum. After two months of conservative therapy the patient was discharged with the diagnosis of Crohn's granulomatous colitis. He was started on a Imuran study (100 mg O.D.).

Four months later he was electively readmitted for reassessment while on the Imuran program. On sigmoidoscopy, perianal erythema, fistula at one o'clock, purulent discharge and linear mucosal ulcers were seen and during this admission his symptoms flared up and his Imuran was discontinued. Prednisone 30 mg daily was instituted and his symptoms abated and he was discharged.

The patient was well for four months but then he was re-admitted for increase in severity of his vomiting, diarrhea, and perianal burning. He had not taken Prednisone regularly prior to admission. This was attributed to his mental dullness. Radiography showed increased deterioration of the colon and for the first time the mucosa of the terminal 4 cm of the ileum was grossly irregular. The patient's condition improved and he was discharged on 30 mg Prednisone with explicit orders on medication routines.

The patient has been coming to OPD regularly with improvement in symptoms and perianal disease.

DISCUSSION

The isolated findings of anosmia and hypogonadotropism have implicated the hypothalamus as the primary lesion in Kallman's syndrome. The strong familial incidence[5] of this syndrome with transmission from mother to son and some female involvement suggests an X-linked dominant gene with partial penetrance. This may suggest that the X chromosome is coded for the hypothalmic releasing factor for the gonadotropic hormones.[6] Early diagnosis and treatment with clomiphene and testosterone has been utilized. The present case had extremely small testes and the trial of testosterone therapy had little effect physically or mentally; and as such was discontinued. This same defect in the hypothalmus must necessarily control olfaction.

The superimposition of an inflammatory bowel disease appears to be unrelated to Kallman's syndrome, although many investigators have shown familial tendencies for Crohn's disease. Treatment for this patient is a problem. With rectum, total colon and terminal ileum involvement, what should be done if surgical intervention became necessary because of obstruction, blind loop, fistulas or perforation. A bypass is not feasible because the distal colon is involved. Ileostomy would be the only possible procedure. Would a mentally defective patient be capable of maintaining a clean functioning ileostomy and assuring adequate nutrition to compensate for his ileostomy drainage? The observation of his progeric facies remains unxeplained.

In summary, 31-year-old male presented with abdominal complaints, diarrhea and pain, and was noticed to have short stature and hypogonadism. He was investigated for his endocrine problem and was diagnosed as hypogonadotropic hypogonadism with anosmia — Kallmann's syndrome. His gastrointestinal complaints progressed and he was investigated and diagnosed as having Crohn's granulomatous colitis with terminal ileal involvement.

ACKNOWLEDGEMENTS

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Clinical Pathological Conference: I

I. Horowitz, 7T2

A 64-Year-Old Man With Renal And Gastrointestinal Dysfunction

A 64-year-old Hungarian male who had immigrated to the United States one-and-a-half years earlier was admitted to hospital complaining of nausea, vomiting and black colored stools for one day.

He had been in good health until two years prior to admission when he developed erysipelas of the left leg which was successfully treated with penicillin. Three weeks later he developed weakness and swelling of the ankles (SOA). At that time he was found to have hematuria and proteinuria (3 gm/24 hours). His BUN, ASO titer and complement were within normal limits. Blood pressure was minimally elevated. His symptoms gradually disappeared over a one month period and the patient was asymptomatic for one year. Six months later he developed easy fatiguability and SOA. One month later, the SOA worsened and constipation associated with guaiac positive stools developed. His hematocrit at that time was 27%. One month later his bowel complaints disappeared but the weakness and SOA persisted. One month later anemia and constipation recurred, now associated with abdominal distention, diarrhea and crampy abdominal pain. Although stools showed no gross blood or mucus, they contained occult blood. One month later the patient was admitted to hospital.

Family history revealed that three of the patient's brothers died of tuberculosis. The patient was pale, his feet were swollen and he had ascites. A chest roentgenogram showed bilateral pleural effusion.

His hemoglobin was 9.8 gm%, hematocrit 28%, reticulocyte count 2.2%, WBC 4,200/mm^3 with a normal differential count. A 24-hour urine contained 848 mg of protein. Total serum protein was 5.4 gm% with 2.7 gm% albumin. Creatinine clearance was 59 ml/minute (normal 70-169). Stools contained occult blood. The serum iron was 38 μgm% and iron binding capacity was 375 μgm%. Serum carotene was 55 mg/100 cc (normal 100-300); D-xylose excretion was 6.9% in five hours (normal 16-33). The alkaline phosphatase was 19 KA and acid phosphatase was 7.2. Blood urea nitrogen, cholesterol, LE preparations were all within normal limits. Bone marrow, liver and renal scans were within normal limits. Sigmoidoscopy revealed changes consistent with colitis.

The patient discharged himself and during the next four weeks his edema and abdominal discomfort worsened.

When admitted this time, physical examination revealed a pale white male. Temperature 96.4°F, pulse 100/minute, blood pressure 100/60. The abdomen was distended, non-tender and soft. Bowel sounds were hypoactive and no organomegaly was found. Rectal examination revealed poor sphincter tone and 4+ guaiac positive stools. Extremeties showed 2+ pedal edema.

Laboratory results revealed: hemoglobin 9.3 gm%, hematocrit 30%, platelets 615,000/mm^3, WBC 2,600/mm^3 with 28% segmented neutrophiles, 45% bands, 26% lymphocytes and 1% monocytes. Red cells showed hypochromasia, anisocytosis and Howell Jolly bodies. Reticulocyte count was 4.3%. Urinalysis showed 2+ protein and 2-4 hyalin casts. The BUN was 43. Alkaline phosphatase was 685 IU, LDH 225, SGOT 250. Electrolytes, glucose, calcium and protein were within normal limits. An electrocardiogram showed right ventricular overload with occasional premature ventricular contractions. Total serum protein was 4.6 gm% with 2.22 gm% albumin. The alpha$_1$ was 0.28, alpha$_2$ 0.70, beta 0.62, gamma 0.77 gm%.

In hospital, the patient received five units of albumin and two units of whole blood during the second and third days.

A sigmoidoscopy revealed diffuse hemorrhagic proctitis. Treatment with hydrocortisone enemas was initiated. On the morning of the fifth day the patient passed large amounts of red blood per rectum and his blood pressure dropped to 40 systolic. He was transfused with four units of whole blood, but expired shortly afterwards.

CLINICIAN:

We are presented with a complex multi-system problem; a patient who one month after a bout of erysipelas develops an acute nephritis with hematuria. After being asymptomatic for a year he develops a nephrotic syndrome (edema, hypoalbumninemia and proteinuria), abdominal pain and occult gastrointestinal bleeding. The low values of carotenes and D-xylose tests indicates small bowel disease. Sigmoidoscopy revealed colonic disease as well. Thus we seem to have a disease process involving most of the gut. This would rule out causes of occult bleeding such as carcinomas of the colon, and diverticular disease. The question of inflammatory bowel disease, Crohn's disease, arises. But lesions characteristic of that condition were not found at sigmoidoscopy. The anemia in Crohn's disease is usually not due to chronic blood loss as was the case in our patient but rather metabolic failure to incorporate iron into red blood cells.

There are very few conditions in which the whole gut is involved with kidney involvement superimposed. Uremic colitis can easily be ruled out in this patient because the BUN must rise to levels of 150 or more for this to occur. We must be looking for an etiological factor

separate from the GI or urinary tract. Are there any predisposing causes in the patient? He had erysipelas; post-streptococcal glomerulonephritis is a common cause of the nephrotic syndrome. But this does not account for the gastrointestinal condition. While the episode of acute glomerulonephritis was probably due to streptococcus the ensuing nephrosis was probably due to another cause.

Amyloidosis may cause the nephrotic syndrome and gastro-intestinal problems. Amyloidosis may be a complication of many chronic diseases such as tuberculosis, leprosy, Hodgkin's disease, chronic biliary disease and carcinoma. The patient has a positive family history of tuberculosis, and had had pleural effusions. He could have had miliary tuberculosis of the intestines or secondary amyloidosis or both.

Hereditary forms of amyloidosis such as those associated with familial Mediterranean fever are easily ruled out. We are left with the primary amyloidoses, those of unknown etiology and those related to myeloma. Our patient's electrophoretic pattern reveals no M-proteins. But these are not necessary for diagnosing plasma cell dyscrasias. There is no mention of Bence Jones protein in the urine which could easily account for tubular malfunction as indicated by the hyaline casts. From the clinical evidence, so far, my working diagnoses are 1) Primary amyloidosis with a plasma cell dyscrasia, 2) Miliary tuberculosis with secondary amyloidosis. I would like to hear what roentgenograms of the gastrointestinal system and skeleton showed. Was a rectal biopsy performed?

RADIOLOGIST:

Skeletal survey was normal. Barium enema and gall bladder series were normal. An upper gastrointestinal series showed mucosal irregularities of the distal jejunum and proximal ileum "consistent with metastatic disease".

PATHOLOGIST:

A rectal biopsy showed amyloid. The urine was positive for Bence Jones protein of the light chain Kappa type. At the post-mortem all the viscera, liver, kidney, spleen, small and large gut were infiltrated with amyloid. The jejunum and ileum had hemorrhagic ulcerations. There was no myeloma found in the bone marrow, but a diffuse plasmacytosis was observed in all organs. Pathological diagnosis was light chain disease (Kappa) with amyloidosis (Figs. 1 and 2).

CLINICIAN:

This case represents an unusual presentation of a plasma cell dyscrasia. The gastrointestinal complications were severe and ultimately responsible for the death of the patient. Light chains, polypeptide chains of molecular weight 22,000, are structural subunits of immunoglobulins. The two major types, Kappa and Lambda, are common to all immunoglobins. Heavy chains, molecular weights between 55,000 and 70,000, differ among the immunoglobulin classes. An overproduction of the light chain Kappa results in a spill-over into the urine producing tubular dysfunction and hyaline casts. An M-protein which consists of both heavy and light chains may not be seen if heavy chain production is not increased as well.

FIGURE 1. Segment of ileum showing hemorrhagic ulcers.

FIGURE 2. X-section of ileum stained with thioflavine T for amyloid under UV light. x 100

SUMMARY

A patient presented with light chain disease (Kappa) and primary amyloidosis resulting in renal and gastrointestinal dysfunction.

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The author wishes to thank Dr. E. Rubin of the Department of Pathology, Mount Sinai Hospital, New York, for permission to present the case material and the Department of Medical Publications, The Hospital for Sick Children, for assistance in the preparation of the manuscript.

Clinical Pathological Conference: 2

Isadore Horowitz, 7T2

A 58-Year-Old Woman With Malabsorption

A 58-year-old white woman came to hospital because she had had diarrhea for three to four weeks. She stated she had six to nine soft and semi-liquid brown stools per day. They did not float and were not foul smelling. She also complained of fever ranging from 101° F. to 103° F., usually occurring at night and occasionally associated with chills. Prior to admission her physician had prescribed "antibiotics" and Atropine. Her diarrhea stopped, but her fever persisted. She gave no history of hematemesis, melena, jaundice, tuberculosis, diabetes or weight loss. Past history included a total hysterectomy for fibromyomata eleven years previously.

Physical examination revealed a pale thin white female with a BP of 130/80 mm Hg, pulse 90/min, respiratory rate 20/min and a temperature of 98.6° F. Palpation of the neck revealed an egg shaped mass in the submandibular region on the right side. The respiratory and cardiovascular systems were normal. The breasts contained no masses. The abdomen was non tender and soft with no organomegaly. Bowel sounds were hypoactive. A rectal examination was normal. The stools were 4+ guaiac positive. Laboratory studies included a hemoglobin of 8.9 gm%, hematocrit 29% and a WBC 12,200/mm^3 and a bone marrow aspirate was within normal limits. BUN, creatinine, glucose, alkaline phophatase, LDH, prothrombin time, bilirubin, SGOT and electrolytes were normal. The calcium was 8.3 mg%; phosphorous 2.4 mg%, magnesium 1.1 mg%, Fe 24μg% and an iron binding capacity was 222μg%. Cholesterol was 124 mg% and an albumin of 2.1 gm% with normal globulins. Cultures of blood stool, bone marrow, urine were repeatedly negative.

The diarrhea recurred upon discontinuation of Atropine.

The stools were consistently positive for occult blood. A sigmoidoscopy and barium enema were normal. An upper gastrointestinal series was done. A small bowel biopsy was normal. The patient refused any further diagnostic procedures. In view of her worsening condition treatment with strip radiation of the abdomen was initiated. Irradiation of three strips produced no change in the patient's condition; the fever and diarrhea persisted. An exploratory laparotomy was performed and the patient died soon after.

DISCUSSION

Clinician — The history of diarrhea and fever are short. The patient had some adenopathy, occult blood in her stools, iron deficiency anemia, leukocytosis, hypoalbuminemia, and malabsorption. Where is the lesion? With an abnormal D-xylose absorption she must have had some condition affecting the small bowel. The fact that the small-bowel biopsy was negative rules out any diffuse condition causing malabsorption such as tropical sprue, Whipple's disease, and amyloidosis. Some local or multifocal lesion of the small intestine is likely. Fever, anemia and diarrhea favor a diagnosis of Crohn's disease but the patient had no abdominal pain or tenderness. Multiple diverticula with overgrowth of bacteria can produce malabsorption, fever and leukocytosis. More likely, we are dealing here with a mass lesion — neoplastic.

The most important of these tumors is lymphosarcoma (90%). This tumor may ulcerate and the occult blood in the stools will lead to anemia. The tumor also interferes with mucosal fat absorption. If the patient had lymphosarcoma it was extensive. Her neck adenopathy highly suggests lymphosarcoma. Adenocarcinoma is rare and usually located near the ampulla of Vater. The presenting symptoms are usually those of peptic ulcer. The patient with carcinoid tumors usually presents with an intestinal obstruction; whereas the patient with carcinoid syndrome presents with diarrhea, flushing and heart failure. Could our patient have secondaries in her small intestine? This is a possibility; but we found no primary focus; her breasts were clear, her uterus had been removed, her lungs and colon were clear. I suggest the patient had lymphosarcoma involving most of the small intestine. Can we look at the upper gastrointestinal series.

Radiologist — The esophagus and stomach are normal. There are marked irregularities of the jejunum and ileum with thumbprinting and segmentation of the barium in the small bowel. This suggests neoplasm nodular in nature with edema of the wall of intestine, consistent with lymphosarcoma, Hodgkin's disease and metastic disease.

Clinician — There are no other systemic symptoms to suggest Hodgkin's disease. Her physician must have thought she had an early staged lymphoma to have instituted radiation therapy, though it had no effect.

Pathologist — The diagnosis was made as soon as the abdominal cavity was opened. After the laparotomy one further question was asked of the patient. Before she died she admitted to some minor surgery which . . .

Clinician — Excuse me for interrupting, but how long ago had she had her mole removed?

Pathologist — Correct. Sixteen years ago a mole was removed from her back. At necropsy small dark brown ulcerating nodules were observed from duodenum to terminal ileum (Fig. 1). Almost the whole small bowel was replaced with tumor and there was an overgrowth of bacteria present. Lightmicroscopy showed anaplastic conglomerations of dopa-positive for melanin cells in the small intestine, mesenteric, hilar and submandibular lymph nodes (Fig. 2). The gallbladder was also involved. Tissue diagnosis was metastatic melanoma and overgrowth of bacteria in her small intestine.

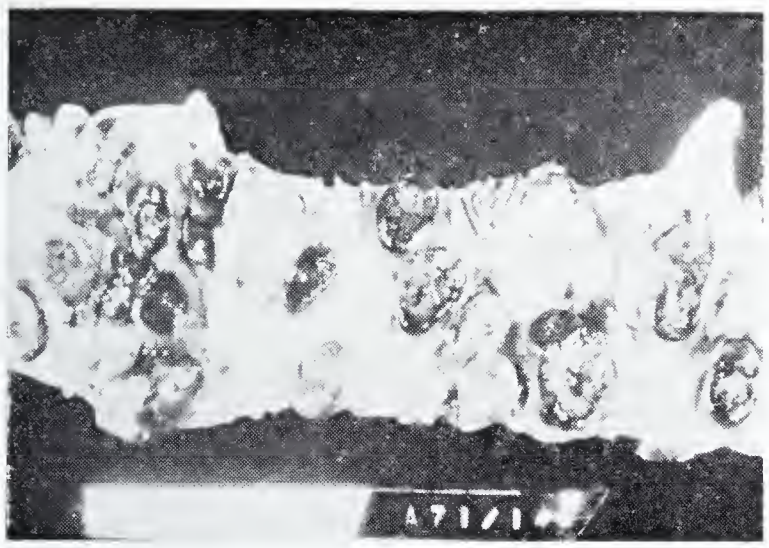

FIGURE 1. Segment of ileum showing well developed ulcerating nodules.

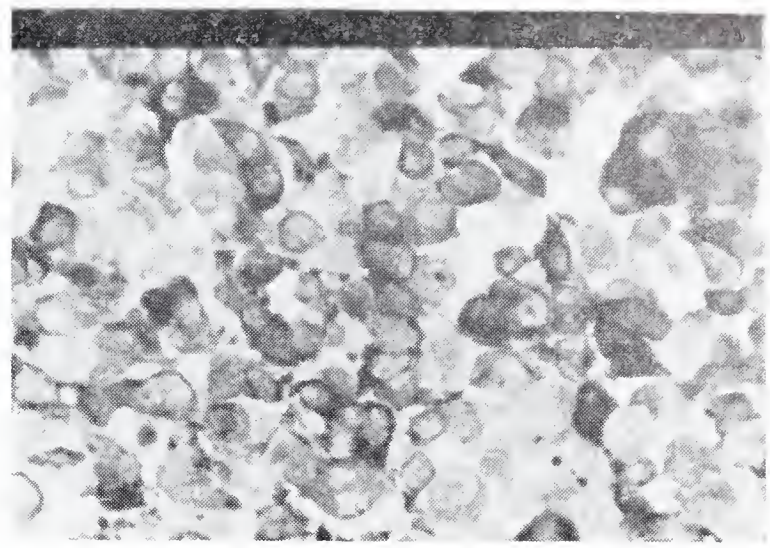

FIGURE 2. Dopa-positive anaplastic cells in nodules in ileum. X700.

CLINICIAN — Sixteen years is an unusually long survival time for a patient with malignant melanoma.

SUMMARY

A 58-year-old lady who had a mole removed 16 years ago presented with fever and malabsorption due to metastatic melanoma and overgrowth of bacteria in her small intestine.

ACKNOWLEDGEMENTS

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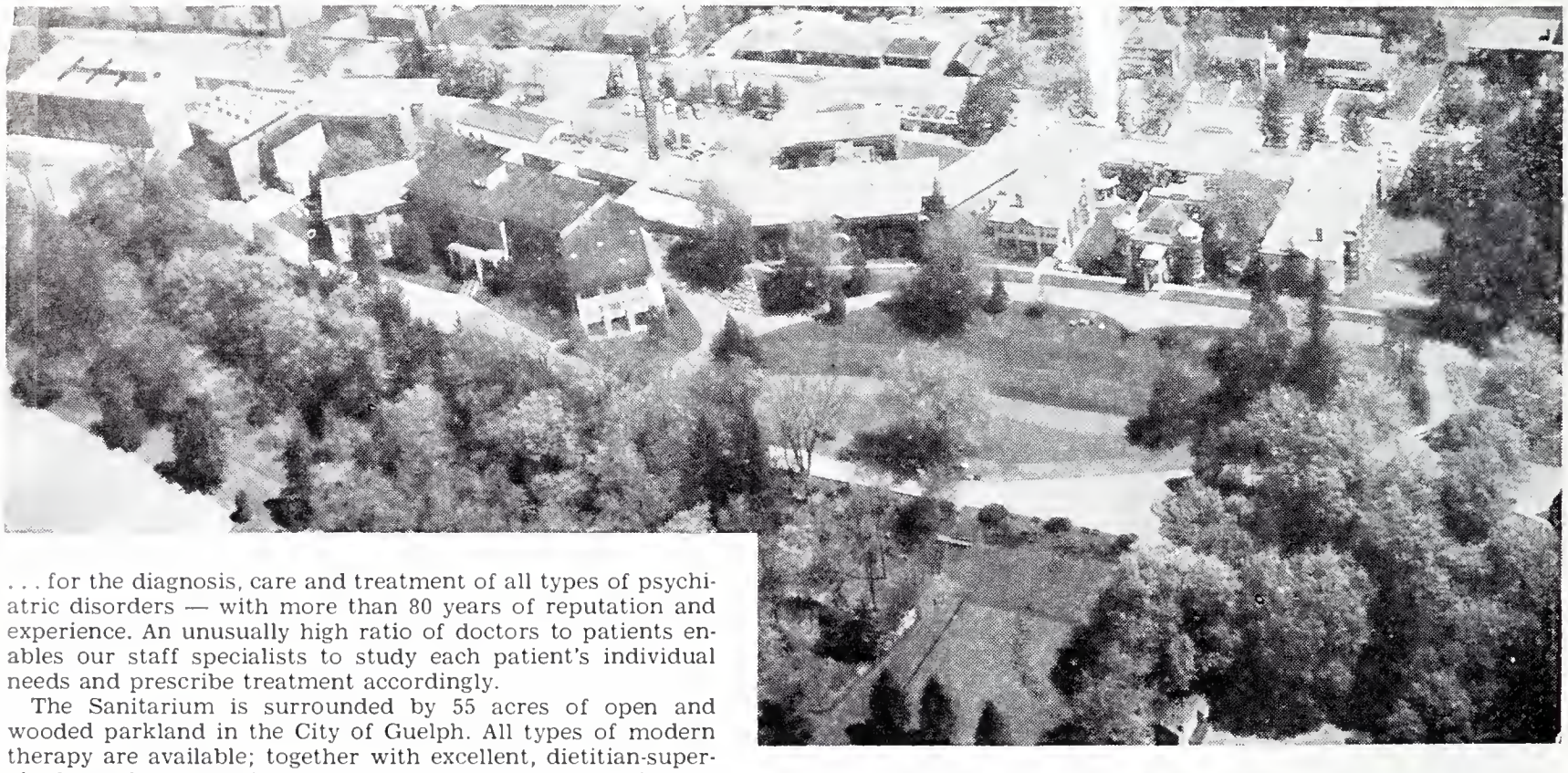

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